AMENDMENTS TO THE DRAWINGS

The Examiner indicated objections to the drawings filed on October 2, 2001. Specifically, the Examiner indicated that the figures contain multiple sections that have not been individually labeled (see Figures 3 and 6-8). The replacement drawing for Figures 3 and 6-8 **filed herewith** are believed to contain all of the necessary corrections.

Attachment: Letter Submitting Drawing Sheet(s) / Four (4) Replacement Drawings

REMARKS

Claims 1-15 are pending in the present application.

The rejection of Claims 1-7 and 10 under 35 U.S.C. §103 over Woghiren et al in view of Shadle et al is respectfully traversed.

The invention of Claim 1 of the present application is a method characterized in that an oligomeric protein having disulfide bonds within a subunit and between subunits, or the subunit peptide constituting said oligomeric protein is denatured in a solution with a protein-denaturing agent, and then the denatured subunit peptide is refolded by removing the denaturing agent from the solution in the presence of polyoxyalkylpolyether having a functional group that reacts with a thiol group. By employing this method, a particularly remarkable effect of providing a monomer peptide derived from oligomeric protein and maintaining an original activity of the subunit and having decreased antigenicity could be obtained (see page 6, line 22 to page 7, line 3 of the specification).

In contrast, Woghiren et al disclose a method of conjugating PEG derivatives with cysteine residues in papain and BPTI. However, these two proteins originally exist as monomers, and therefore they are completely different from the oligomeric protein or the subunit peptide constituting said oligomeric protein to which the method of the present invention can be applied. In addition, the method disclosed by Woghiren et al does not involve a procedure of denaturing a protein or a peptide by using a protein-denaturing agent.

Shadle et al disclose a method of binding PEG derivatives having maleimide groups to a modified CSF-1 molecule, which is a dimeric protein comprising a modified subunit with artificially-introduced cysteine residues and a native subunit. The modified subunit and the native subunit were purified in the presence of a protein-denaturing agent, and then subjected

to refolding process for the formation of dimer (see column 10, lines 35-36). Subsequently, the dimeric protein formed was conjugated to the PEG derivative (see column 11, lines 63-68). Specifically, in the method disclosed by Shadle et al the refolding was conducted so as to establish the biologically active dimeric configuration (see column 10, lines 57-62), and the PEG derivative was not involved in the refolding process. Further, the desired PEG-bound protein was a dimeric protein, not a monomeric subunit peptide as is disclosed in the present invention.

As described above, the subject proteins or peptides of the methods of Woghiren et al or Shadle et al are completely different from the oligomeric protein or the peptide constituting said oligomeric protein which is the subject of the present invention. In addition, neither Woghiren et al nor Shadle et al. suggests the technical feature of the present invention, in which a denatured subunit peptide reacts with polyoxyalkyl polyether while refolding the denatured subunit peptide by removing the denaturing agent from the solution containing the denatured subunit peptide. Therefore, Applicants submit that it is unlikely that one of ordinary skill in the art could have easily conceived the present invention based on the disclosures of Woghiren et al and Shadle et al. Thus, Applicants submit that the invention as claimed in Claims 1-7 and 10 of the present application is not obvious over Woghiren et al, in view of Shadle et al.

In view of the foregoing, withdrawal of this ground of rejection is requested.

The rejection of Claim 8 under 35 U.S.C. §103 over Woghiren et al in view of Shadle et al and Deng et al is respectfully traversed.

The invention of Claim 8 of the present application is a method characterized in that the subunit peptide obtained by the method of Claim 1 of the present application has an

activity of inhibiting a physiological activity of the oligomeric protein from which the subunit peptide originated.

Woghiren et al and Shadle et al and the deficiencies are discussed above. Further it is submitted that Deng et al disclose a mutant CSF-1 in which cysteine residues in its subunit peptide are substituted. However, Deng et al do not disclose or suggest that the mutant subunit peptide actually inhibited the biological activity of the wild type dimeric protein, but only show that the cells expressing the mutant CSF-1 proteins did not exhibit detectable CSF-1 activity (see Table 1).

Therefore, it would not have been obvious for one of ordinary skill in the art that a subunit peptide having an activity of inhibiting a physiological activity of an oligomeric protein from which the subunit peptide originates could be obtained by binding polyoxyalkyl polyether to cysteine residues in the subunit peptide that constitutes the oligomeric protein. Thus, Applicants submit that the invention as claimed in Claim 8 of the present application is not obvious over Woghiren et al, in view of Shadle et al and Deng et al.

In view of the foregoing, withdrawal of this ground of rejection is requested.

The rejection of Claims 1 and 9 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

The Examiner rejected Claim 1 alleging that step (b) is unclear. To address this criticism Applicants have amended Claim 1 to add a phrase which clarifies that the subunit peptide binds to the polyoxyalkyl polyether via the reaction between the thiol group of the subunit peptide and the functional group of the polyoxyalkyl polyether that reacts with a thiol group. This amendment is supported by the last paragraph of page 18 of the specification.

Claim 1 has also been amended to replace the term "producing" with "purifying" as suggested by the Examiner.

The Examiner rejected Claim 9 alleging that it is unclear whether the polyoxyalkyl polyether is bonded to cysteine residues that are involved in intermolecular or intramolecular or both interactions. To address this criticism, Applicants have amended Claim 9 to clarify that the polyoxyalkyl polyether is bonded to a cysteine residue of the subunit peptide that is originally involved in formation of a disulfide bond between subunits in the oligomeric protein.

In view of the amendments herein, Applicants request withdrawal of this ground of rejection.

The objections to the specification are obviated by amendment. Applicants have amended the specification and submit herewith corrected drawings to address the Examiner's various points of criticism. Withdrawal of this ground of objection is requested.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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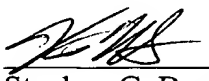

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